Marcia Mulkey September 9, 1999
Director, Office of Pesticide Programs
Mail Code 7501C

Ms. Mulkey,

Again, I find the need to advise you, as OPP Director, of what I perceive to be unacceptable activities within OPP over the disposition of the Science Policy on the use of cholinesterase inhibition for risk assessments. This is a very complicated subject, both scientifically and administratively, which I am unable to characterize adequately in a brief letter of this sort. Nontheless, the facts need to be set forth, even though in abbreviated and incomplete form, in a quest for corrective action.

I might remind you of past events by saying a certain group of individuals in HED developed and presented a Science Policy to the SAP in 1997. The SAP supported that policy. Since that time essentially the same policy accompanied by its supporting documentation was reissued on November 5, 1998 for public comment, particularly as the policy related to FQPA issues. The same HED workgroup individuals who developed the policy for the 1997 SAP meeting reviewed the new public comments and participated in revising the Policy statement accordingly. The comments I drafted with respect to that activity were dated March 23, 1999, a copy of which would be available upon request.

Now, much to my surprise, I received via cc-mail on August 19, 1999 a copy of a remarkably different draft Policy statement from HED seeking almost in passing, comments within one week from certain individuals including those of the so called "origional workgroup", myself so identified. See the attached August 19 cc-mail notice. (Attachment 1) One must conclude from this that there is now a *new workgroup*, consisting from my perspective of unidentified personages, which is now writing the Policy, obviously under the direction or approval of OPPTS management. I must say I personally view this handling of the matter disrespectful of those who have had a long involvement with the cholinesterase project. The personnel who have suffered this demise have done no wrong, indeed have only fulfilled their duties in an exemplary and competent manner in developing a policy out of a very complex scientific and political quagmire that existed prior to the 1997 SAP. Their work received SAP's most laudable and indisputable support. The current, i.e. August 18, 1999 draft Policy, is an aberration of that which has been accomplished, and its genesis inexplicable.

A copy of my August 25, 1999 comments developed in response to the August 19 request is attached. (Attachment 2)

The following are additional important points I wish to offer with respect to the August 18 draft

Policy:

1) In contrast to the earlier versions, there are now no acknowledgements for the origional or new workgroup on the policy development. People who have worked so long and been so instrumental in developing a reliable Policy deserve such recognition.

2) The background document (Dementi 1997), hereinafter referred to as the Background Document (1997), which serves as the scientific basis for the Policy has been excluded from attribution as such in the text of the revised Policy and from the bibliography, again in contrast to the origional Policy. I should advise that the 1997 SAP characterized the Background Document (1997) as excellent, and I find no documentation in the revised Policy to the contrary. I must admit at this point it is with a certain degree of awkwardness I feel in defending my own work in this way, but the fact remains I have worked a long time on this project and I have seen no refutation of the work's conclusions. I must reiterate here the view I expressed in my August 25 comments, namely the August 18 revised Policy *has not and cannot imply any* endosement of the 1997 SAP. This should be acknowledged. Nor to my knowledge does it have any other level of legitimate external scientific peer review.

3) The August 18 revised Policy statement acknowledges (p. 4) as its guiding principles the National Academy of Sciences (NAS) 1983/1994 paradigm for risk assessment and risk management practices. Now NAS enunciates many principles, certainly one of the most important being the separation of the Risk Assessment and Risk Management procedures. Accordingly, the National Research Council (1996) says "The authors of the Red Book (meaning the 1983 NAS report) advocated a clear conceptual distinction between risk assessment and risk management, noting, for instance, that maintaining the distinction between the two *would help to prevent the tailoring of risk assessments to the political feasibility of regulating the substance in question* (emphasis added)" (p. 5) The document goes on to say, however, the choice of risk-assessment techniques should not be isolated from society's risk-management goals. I must say at this point, and I would like to be proved mistaken, that the precipitous replacement of the "origional workgroup" on the cholinesterase policy, with unnamed individuals, and the radical changes of the well thought out and SAP (1997) approved Policy with its supporting documentation can only represent a form of management intrusion into the process, and indeed outside the purview of external expert scientists in the field, and thus violates the very principles of the National Academy of Sciences being cited.

4) The August 18 revised Policy moved away from reliance upon plasma cholinesterase for regulatory purposes despite evidence and support of the SAP(1997) to the contrary. There is no documentation presented to justify this change, only nameless public comments that no one such as myself has been accorded the opportunity to evaluate, or even know of with regard to their precise identity. In my August 25 comments, I summarized certain reasons presented in the Background Document (1997) as to why plasma cholinesterase inhibition should serve as a regulatable end point until substantiated otherwise by definitive data on the particular cholinesterase inhibitor in question. I feel inclined at this point to present more evidence substantiating the importance of plasma cholinesterase inhibition.

Please see appended (Attachment 3) a copy of selected pages from my personal copy of the National Academy of Sciences' National Research Council, NRC (1993) report "Pesticides in the Diets of

Infants and Children", which did not merit citation in the August 18 draft Policy statement. As you know this document, perhaps more than any other, spawned the FQPA (1996). I should note that a principle rationale for the NRC's conclusion that children may be particularly vulnerable to organophosphate cholinesterase inhibitors in their diets was rationalized on the basis of a "*common toxic effect*", identified as *plasma cholinesterase inhibition*, resulting from the concerted effects of five such agents, namely: acephate, chlorpyrifos, dimethoate, disulfaton and ethion. See pages 6 and 297. In electing this end point NRC (1993) says: "This method was used to determine how many children are likely to be exposed to unsafe levels of multiple pesticides with that common effect......." (p. 297) Now members of our "new workgroup" might argue NRC committee members did not appreciate, as does the workgroup, the relative unimportance of plasma cholinesterase inhibition as a legitimate end point of concern. But where is the evidence? I should note further the members of the NRC group drafting this report, like the SAP (1997) are recognized national experts in the field. The point is that plasma cholinesterase inhibition is an anticipated response upon exposure to a chemical substance designed as an acetylcholinesterase inhibitor to be lethal to insects and other pests. Hence, the finding of plasma cholinesterase inhibition constitutes expected and sufficient evidence of the presence within the host of the acetylcholinesterase inhibitor in question. Assessments of the magnitude of inhibition of acetylcholinesterase within the host's CNS, including its many regions and sub-regions, to this point in time lacks rigor in most data sets, and that for the PNS is altogether absent.

One should also note that while the so-called blood-brain barrier may accord some variable protection for the many individual cholinesterase inhibiting compounds as noted in the August 18 revised policy statement (pp. 6 and 13), this policy statement neglects to advise it may not be well developed in infants and children. NRC (1993) says: "There is speculation that neonates and infants may be more susceptible to chemically induced neurotoxicity, in part because of the immaturity of their blood-brain barrier. Watanabe et al (1990) point out that the central nervous system in developing individuals is potentially vulnerable to chemicals for a protracted period because the central nervous system requires longer than most other organ systems for cellular differentiation, growth, and functional organization. Therefore, any increase in accessibility to cytotoxic agents because of delayed maturation of the blood-brain barrier could have serious consequences." (p. 89) Currently OPP gathers no data on the relative accessability of these inhibitors to the CNS of adult versus young individuals. So this is another reason to be concerned over potential greater sensitivities of children, and why it is important, particularly in the case of infants and children to place reliance upon the most sensitive indicator of exposure to a cholinesterase inhibitor, including plasma cholinesterase inhibition.

5) The draft Policy when speaking of the blood-brain barrier, neglected to mention a publication by Friedman et al (1996), cited in the Background D ocument (1997), to the effect that the integrity of this interface may be compromised by stress.

6) Where the vulnerability of children is concerned, a topic ignored in the August 18 draft Policy statement, the NRC (1993) says: "At present, to provide added protection during early development, a third uncertainty factor of 10 is applied to the NOEL to develop the RfD. This third 10-fold factor has been applied by the EPA and FDA whenever toxicity studies and metabolic/disposition studies have shown fetal developmental effects. Because there exist specific periods of vulnerability during postnatal development, the committee recommends that an uncertainty factor up to the 10-fold factor

traditionally used by EPA and FDA for fetal developmental toxicity should also be considered when there is evidence of postnatal developmental toxicity *and when data from toxicity testing relative to children are incomplete* (emphasis added)" (p. 9) "In the absence of data to the contrary, there should be a presumption of greater toxicity to infants and children." (p. 9) NRC (1993) also says: " Assessment of the effects of pesticides on the developing human nervous system is difficult because the methodology for such assessment is complex and poorly delineated. Development of the CNS is characterized by exacting architectural complexity and localization of function occurring over a prolonged period postnatally. The effects of altered neurologic development may be measured either as anatomic or behavioral and cognitive outcomes." (p. 108) Through the use of these quotations, I seek to strengthen that which I presented in my August 25 comments, namely that in the absence of cholinesterase data in the developmental toxicity and reproduction studies, such studies are *incomplete* and, hence, are fundamentally flawed with respect to their employment in decisions as to whether to delete or modify the FQPA imposed additional 10X factor, which likely finds its genesis in those quotations given above fron the NRC (1993) report. It should also be self-evident that plasma cholinesterase inhibition, providing as it does evidence of the presence of an acetylcholinesterase inhibitor in the host, cannot be ignored should it be the most sensitive indicator of an effect, lacking adequate neural cholinesterase data.

The August 18 draft Policy acknowledges that: "In 1998, as part of the Tolerance Reassessment Advisory Committee (TRAC) review process for science policy issues, OPP published the 1997 policy paper for public comment (USEPA, 1998b). The present science policy guidance has been prepared considering the comments received from the SAP and the public in 1997 and during the public comment period in 1998." (p. 8) I believe this statement should have said that the focus for 1998 comment period was the "science policy issues"**related to the Food Quality Protection Act**. This is very important because contrary to the claims made in this quotation, the August 18 draft Policy largely ignores FQPA issues responded to in the 1998/99 comment period.

Accordingly, two important questions included in that November 5, 1998 FR notice were: 1) question #5: "Should comparative data on ChEI in the young exposed pre-natally, during infancy (nursing), and during childhood be considered essential for defining the relative sensitivity of the young and adults?"; and 2) question #6: "Are other measures, such as functional measures of clinical signs, or learning and memory, similarly important?" Public commenters responded to these questions, and the April 9, 1999 draft Policy addressed these. Yet, there is *not even an acknowledgement of these questions or public comments* in the August 18 draft Policy.

That which should be said with respect to these two very important questions are to be found on pages 20-21 of HED's April 9, 1999 draft: "The Agency's Responses to Public Comments on the Draft FQPA Science Policy Document: Office of Pesticide Programs Science Policy on the Use of Cholinesterase Inhibition for Risk Assessments of Organophosphate and Carbamate Pesticides". It should be recognized that these two questions (#s 5 and 6) were included in the November 5, 1998 notice as a way of seeking guidance as to how the policy would address FQPA concerns regarding relative sensitivities or young and developing versus mature individuals. The April 9, 1999 draft says with respect to these questions: "There is a growing literature on the effects of early exposures on cholinesterase inhibition and neurobehavioral measures. In more recent developmental neurotoxicity studies, cholinesterase inhibition has been assessed in both dams and offspring, as well as the variety of functional tests, including learning and memory tasks, that are included in that guideline. While the larger issues of the scope of requirement of developmental neurotoxicity studies or other related studies are beyond the scope of this review of cholinesterase policy, for cholinesterase inhibitors, measures of cholinesterase inhibition and assessment of cholinergic functions (which includes learning and memory) are specifically appropriate and important to the evaluation of these classes of chemicals." (p. 21) The neglect of the August 18 draft Policy to incorporate these considerations, while claiming it incorporats consideration of the public comments to the 1998 FR notice is of peculiar concern, and I fear indicative of the intrusion of management into risk assessment activities, contrary to the NAS principles cited by the August 18 draft Policy itself.

Thank you for your consideration of these views.

Sincerely,

Brian Dementi, Ph.D., DABT
Senior Toxicologist

Attachments (3)

References:

National Research Council (1996): Science and Judgement in Risk Assessment (Student Edition). Taylor & Francis Publishers, Washington DC

National Research Council (1993): Pesticides in the Diets of Infants and Children. National Academy Press, Washington DC